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Anxiety and Heart Disease

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Despite impressive gains made in the treatment of coronary heart disease (CHD), it remains the number one cause of death and a major cause of disability among women and men in the United States. By the year 2020, CHD is projected to be the number one cause of death worldwide.(American Heart Association, 2002; Chockalingam et al., 2000; Reddy & Yusuf, 1998) Coronary heart disease claims more lives each year than the next five causes of death combined.(American Heart Association, 2002) The effect of various demographic (e.g., age, gender) and clinical (e.g., presence of comorbidities) characteristics on development of cardiac events and on recovery has been well-studied.(Breithardt et al., 1995) These demographic and clinical characteristics are used commonly in clinical practice to determine patient risk for future events.

Far less attention has been paid to the impact of psychological risk factors despite compelling evidence that they confer equal and, in some cases, greater risk than demographic or clinical risk factors.(Kubzansky & Kawachi, 2000; Kubzansky, Kawachi, Weiss, & Sparrow, 1998b; Rozanski, Blumenthal, & Kaplan, 1999a) Failure to understand and address psychological risk factors for CHD events may be one reason that CHD morbidity and mortality remain so high. Anxiety disorders are among the most prevalent psychiatric disorders. (Kubzansky et al., 1998b) Given the prevalence of anxiety in the general population and in patients with CHD, the potential public health impact for preventing CHD development and progression is high if the nature of the relationship between anxiety and CHD is appreciated.

Anxiety.

Anxiety is a negative affective state resulting from an individual's perception of threat and characterized by a perceived inability to predict, control or gain the preferred results in given situations.(Barlow, 1988) Anxiety is a distinct emotional experience that has cognitive, neurobiological and behavioral components, and that arises out of the interaction of an individual with the environment. (Kubzansky et al., 1998b) It, like other emotions, allows flexibility in behavioral responses to a changing environment. Anxiety is considered an adaptive process until its magnitude or persistence render it a dysfunctional response that can have negative consequences.

Anxiety exists on a continuum from normal to pathological, and there are a number of anxiety disorders (i.e. panic disorder, phobic anxiety, generalized anxiety, anxiety reactions, chronic anxiety).(Barlow, 1988; Kubzansky et al., 1998b) Nonetheless, research to date strongly suggests that anxiety along the continuum from normal anxiety reactions to pathological have comparable cognitive, neurobiological, and behavioral components, and that clinical anxiety and sub-clinical anxiety are not fundamentally different phenomena.(Barlow, 1988; Kubzansky et al., 1998b; Lewis & Haviland, 1993; T. W. Smith & J. M. Ruiz, 2002) Thus, the potential link between anxiety and risk for CHD events has ramifications for a larger number of individuals who would not normally be diagnosed with clinical anxiety.(Kubzansky et al., 1997; Kubzansky et al., 1998b; T. W. Smith & J. M. Ruiz, 2002)

Anxiety in individuals with CHD.

Anxiety is common among individuals with chronic CHD and among those recovering from acute cardiac events.(Crowe, Runions, Ebbesen, Oldridge, & Streiner, 1996; Januzzi, Stern, Pasternak, & DeSanctis, 2000a; Kubzansky et al., 1998b; Malan,

1992; Moser & Dracup, 1996; D. K. Moser, S. McKinley, B. Riegel, L. V. Doering, & B. J. Garvin, 2002; Sirois & Burg, 2003b) In fact, anxiety is more common than depression.(Januzzi et al., 2000a) The prevalence of anxiety is approximately 70-80% among patients suffering an acute cardiac event and chronically persists in about 20-25% of individuals with CHD.(Crowe et al., 1996; Moser & Dracup, 1996; D.K. Moser et al., 2002) Even among individuals with CHD who have never had an event, the prevalence of anxiety is 20-25%.(Januzzi et al., 2000a) Although anxiety is an expected and even normal reaction to an acute cardiac event or the threats of living with a chronic illness, anxiety is not benign if it persists or is extreme.(Januzzi et al., 2000a; Kubzansky & Kawachi, 2000; Kubzansky et al., 1997; Kubzansky et al., 1998b; Malan, 1992; R. A. Mayou et al., 2000; Moser & Dracup, 1995; Rozanski et al., 1988b; Rozanski et al., 1999a; Rozanski, Krantz, & Bairey, 1991a)

Anxiety can hinder psychosocial adaptation to CHD and physical recovery after an acute event. Anxiety predicts poorer quality of life for CHD patients in the short and long-term.(Lane, Carroll, Ring, Beevers, & Lip, 2000a, 2000b, 2001a; R. A. Mayou et al., 2000) Anxiety hinders psychosocial adaptation by interfering with patients' self-care abilities.(Maeland & Havik, 1989; Malan, 1992) Patients who are too anxious frequently are unable to learn or act upon new information about necessary life-style changes.(Rose, Conn, & Rodeman, 1994) Anxious patients experience problems coping with challenges, and anxiety adversely affects adherence and rehabilitation efforts.(Lane, Carroll, Ring, Beevers, & Lip, 2001b; Maeland & Havik, 1989; Rose et al., 1994) Persistent anxiety predicts worse disability, more physical symptoms and poorer functional status in CHD patients.(Sullivan, LaCroix, Baum, Grothaus, & Katon, 1997; Sullivan, LaCroix, Spertus,

& Hecht, 2000) Anxious CHD patients return to work slower or less often than non-anxious patients(Havik & Maeland, 1990), and have more problems resuming sexual activity after an acute event.(Rosal, Downing, Littman, & Ahern, 1994) Patients with sustained anxiety may suffer from "cardiac invalidism", an older term that still describes a subset of CHD patients whose level and debilitation or disability after a CHD diagnosis or acute event is unexplained by the severity of their physical condition.(Sullivan et al., 1997; Sullivan et al., 2000; Sykes, Evans, Boyle, McIlmoyle, & Salathia, 1989)

Despite the importance of anxiety to recovery in patients with CHD and in particular with acute myocardial infarction (AMI), few investigators have examined the phenomenon. Our research team has focused on studying anxiety in AMI patients and results of our studies are discussed below.

Anxiety after acute myocardial infarction.

Prevalence of anxiety in an international sample. Investigators from North America reported that 10% to 26% of patients with AMI had higher levels of anxiety than patients with a psychiatric disorder.(Crowe et al., 1996; Moser & Dracup, 1996) However, the prevalence of anxiety after AMI has not been studied extensively among international populations. Additionally, no investigators have evaluated whether the psychosocial or physiologic factors that are related to anxiety interact with the unique cultures within each country to produce a differential impact on anxiety.

Understanding anxiety from an international perspective is important because anxiety poses a significant risk to patients after AMI. This risk may result from activation of the sympathetic nervous system and hypothalamic-pituitary-adrenal (HPA) axis.(Sirois & Burg, 2003b) Investigators have shown that anxiety after AMI is

associated with increased in-hospital complications such as lethal dysrhythmias, continued ischemia, and reinfarction.(Moser & Dracup, 1996) Furthermore, anxiety has been shown to predict future coronary events and long-term survival after AMI.(Denollet & Brutsaert, 1998; Frasure-Smith, Lesperance, & Talajic, 1995b; Thomas, Friedmann, Wimbush, & Schron, 1997) However, individuals from different ethnic and cultural backgrounds may vary in their biological response to anxiety.(Lin, 2001)

People from all cultures and countries experience anxiety.(Lepine, 2001a) Furthermore, culture influences the perception of a stress-producing situation, symptoms of stress, and the expression of emotions.(Kirmayer, 2001) We conducted a study were to evaluate whether anxiety after AMI differs across five countries and to determine whether an interaction between country, and sociodemographic and clinical variables contributes to variations in the expression of anxiety.(DeJong et al., in press)

This study was a prospective, comparative, cross-cultural investigation of anxiety early after AMI in five countries. The participants' anxiety level was assessed within the first 72 hours of hospital admission. Participants were recruited from community hospitals and academic medical centers from five countries – Australia, England, Japan, South Korea, and the United States (U.S.). Eligibility criteria for participation in this study included: 1) documented AMI by elevated cardiac isoenzymes and typical ECG changes; 2) onset of AMI outside of the hospital or other institutional setting, such as an extended care facility; 3) hemodynamic stability and absence of pain at the time of interview; and 4) intact cognitive function that allowed the participant to answer questions concerning their emotional status. Participants with life-threatening or debilitating co-morbidities were excluded from the study.

Data were collected by experienced cardiovascular nurses who interviewed each participant within 72 hours (mean 53 ± 38 hours) of admission to the hospital. The research assistants collected sociodemographic and clinical data. Anxiety was measured using the Anxiety Subscale of the Brief Symptom Inventory to measure patients' perception of their current level of anxiety. Although concise, the 6-item subscale is a reliable, and valid measure of state anxiety in acutely ill persons.(L. R. Derogatis & Melisaratos, 1983) The Anxiety Subscale of the Brief Symptom Inventory was selected because it minimizes participant burden, is reliable and valid, was conceptually relatively easy to translate from English to Korean and Japanese, and does not include physical indicators of anxiety. Using a scale of 0 to 4 (0 = "not at all" and 4 = "extremely"), participants rate their level of emotional stress related to six items. The averaged score represents the participant's overall level of state anxiety, thus, mean scores can range from 0 to 4. High standard deviations are common and reflect variability in the samples studied.(L. R. Derogatis & Melisaratos, 1983) Native speaking researchers translated the Anxiety Subscale of the Brief Symptom Inventory from English into Korean and Japanese to ensure linguistic and cultural equivalence. A second native speaking researcher translated the instruments back into English to ensure that the translation process did not distort the meaning of the instruments.

To compare baseline differences in sociodemographic and clinical characteristics among countries, one-way analysis of variance (ANOVA) or chi-square were used as appropriate to the level of measurement. Multifactorial analysis of covariance (ANCOVA) was used to evaluate whether there were differences in mean anxiety scores among the five countries while correcting for sociodemographic characteristics upon

which the countries differed. Additionally, multifactorial ANCOVA was used to evaluate whether sociodemographic and clinical characteristics interacted with country to produce a differential impact on anxiety.

A total of 912 AMI patients participated in this study; 127 from Australia, 144 from England, 136 from Japan, 128 from South Korea, and 377 from the U.S. Sociodemographic and clinical characteristics of the sample, by country are presented in Tables 1 and 2.

The mean level of anxiety in the entire sample was 0.62 ± 0.76 (range 0 to 3.83), which is 44% higher than the normal mean level of 0.35 reported in a sample of healthy adults. [16] Levels in each country are illustrated in Figure 1. The mean levels of anxiety in each country were as follows: 0.54 in Australia (this anxiety level is 54% higher than normal); 0.47 in England (34% higher than normal); 0.66 in Japan (89% higher than normal); 0.64 in South Korea (83% higher than normal); and 0.69 in the U.S (97% higher than normal).

In all countries, patients reported high anxiety levels. A total of 46%, 35%, 43%, 52%, and 50% of patients in Australia, England, Japan, South Korea and the U.S. respectively reported anxiety levels higher than the normal reference mean. A total of 7%, 7%, 15%, 5%, and 10% of patients in Australia, England, Japan, South Korea and the U.S. respectively reported anxiety levels higher than the mean of 1.7 reported for psychiatric in-patients.(L. R. Derogatis & Melisaratos, 1983)

Although there was a significant difference in anxiety level among the countries ($P = .03$) on the overall ANOVA, post hoc testing to discover where the countries differed using the Bonferroni test revealed that only England and the U.S. ($P = .03$)

differed. Patients in England reported lower levels of anxiety than patients in the U.S. This difference in anxiety level disappeared after controlling for sociodemographic variables on which the countries differed.

The following sociodemographic and clinical characteristics were examined to determine if they interacted with country to influence anxiety: age, gender, marital status, education level, medical history, Killip classification on admission, use of various therapies in the emergency department and pain level. None of these variables interacted with country to affect anxiety.

The principal findings from this study were that anxiety level early after AMI was high among patients from five diverse countries on four continents and did not differ substantially by country. Although, patients from England reported anxiety levels lower than those from the U.S., there were no differences among any of the other countries, and the difference between English and American patients disappeared after correction for sociodemographic variables on which the countries differed.

To our knowledge, this is the first cross-cultural comparison of anxiety levels in AMI patients early after the acute event. These findings demonstrate that, despite the potential influence of culture on emotion, (Draguns & Tanaka-Matsumi, 2003; Kirmayer, 2001; Taylor-Piliae & Molassiotis, 2001) patients suffering AMI display a similar emotional response to this potentially life-threatening event. If culture influences the experience, expression and communication of emotion, (Leff, 1973) why did we fail to find a difference in the expression of anxiety among patients from these five culturally diverse countries? Anxiety is thought to be a universal emotion found in all societies, but the expression and communication of anxiety are believed to be culturally different.

However, Mesquita and Frijda, in a comprehensive review of cultural variation in emotions,(Mesquita & Frijda, 1992) argue that there are little data from which one can conclusively state that there are cultural variations in emotion. Depending on the theoretical framework from which one's view arises, there are data to support the notion that emotions are universal and data to support the notion that emotions are social constructs.(Mesquita & Frijda, 1992) They further note that most of the research on cross-cultural comparisons of emotions considered only abstract representations of emotions and not concrete representations, such as the specific threat of physical illness. Thus, the expectation that there are cultural differences in the expression of anxiety may be unfounded.

Little cross-cultural research has been conducted to examine the emotions of patients after AMI. Scherer reported that among European, Japanese, and American university students, Japanese students were less fearful and more reserved about expressing their fear and exhibited a diminished physiological response to fear.(Scherer, Wallbott, Matsumoto, & Kudoh, 1988) In contrast, others found that Chinese men who underwent cardiac catheterization and Taiwanese patients with AMI reported similar levels of anxiety as American patients.(Chiou, Potempa, & Buschmann, 1997; Taylor-Piliae & Molassiotis, 2001) In an epidemiologic review, Lepine pointed out that anxiety disorders are found in all countries that were studied.(Lepine, 2001b) Additionally, somatization of anxiety appears to be a common reaction across a variety of cultures.(Kirmayer, 2001) Anticipation of physical danger has been reported as a precursor of anxiety in both non-Western and Western cultures.(Mesquita & Frijda, 1992) Therefore, our finding that patients with AMI from five diverse countries

expressed similar levels of anxiety suggests that the threatening nature of AMI produces anxiety regardless of the patient's culture.

The high anxiety level seen among patients in all countries is of concern for a number of reasons. The level of anxiety seen, even in patients from the country with the lowest mean anxiety level is substantially higher than that seen in healthy individuals.(L. P. Derogatis, 1993) For both humanistic and clinical reasons, it is essential to address this level of anxiety. Anxiety in cardiac patients is associated independently with higher short- and long-term morbidity and mortality.(Frasure-Smith et al., 1995b) Patients with higher anxiety early after AMI have a longer stay in the cardiac care unit and hospital,(Lane et al., 2001a; Legault, Joffe, & Armstrong, 1992) report sustained anxiety and long-term distress, suffer more symptoms irrespective of the severity of their physical condition(R. Mayou, 2000), consume more health care resources(R. Mayou, 2000), and report a lower quality of life(Brown et al., 1999; Lane et al., 2001a; R. A. Mayou et al., 2000) than patients with lower anxiety.

We investigated the possibility that a number of clinical or sociodemographic factors that might affect anxiety level would interact with country to affect anxiety level. None of the multiple factors examined produced a differential effect on anxiety. This finding suggests that, among AMI patients, anxiety is common regardless of clinical presentation, presence of co-morbidities or severity of AMI, and that it can not be predicted by typical sociodemographic or clinical characteristics. Further research is warranted to determine factors that may moderate anxiety in order to better understand the phenomenon among AMI patients and develop effective interventions.

In summary, patients from each country studied experienced high anxiety after AMI. Even though various cultures were represented in this study, culture itself did not account for variations in anxiety after AMI. It appears that anxiety after AMI is a universal phenomenon. Given the potentially negative impact of anxiety on mortality and quality of life after AMI, clinicians and researchers should continue to explore interventions to treat anxiety and minimize its untoward effects.

Gender differences in anxiety.

It is important that gender differences in anxiety after AMI be explored because high anxiety is associated with poorer AMI recovery and interventions to decrease anxiety levels should be targeted appropriately to those with the highest levels. It is equally important to explore gender differences internationally to improve planning of international public health initiatives and planning of health priorities and initiatives in the United States, which has an increasingly diverse population. Accordingly, we conducted a study to determine whether there are gender differences in anxiety, when measured early after AMI, in an international sample.(Moser et al., 2003)

The sample, measurement and data collection procedures are described above and in the full publication.(Moser et al., 2003) In this prospective, comparative study, 912 AMI patients were enrolled from Australia, South Korea, Japan, England, and the United States. Briefly, we used the anxiety subscale of the BSI to assess anxiety level within 72 hours of an admission for confirmed AMI.

Sociodemographic and clinical characteristics of patients at the different sites are compared by gender in Table 3. The mean level of anxiety reported for the entire sample was 44% higher than the normative anxiety score for adults. Sixteen percent of women

in this sample versus 8 percent of men reported levels of anxiety higher than that seen in psychiatric patients. The range reported was 0 to 3.83. For reference purposes, the published norm for non-patient subjects is 0.35 ± 0.45, for psychiatric inpatients is 1.5 ± 1.1 and for psychiatric outpatients is 1.7 ± 1.0.(L. P. Derogatis, 1993; L. R. Derogatis & Melisaratos, 1983) Gender specific values for male and female psychiatric outpatients have been reported at 1.5 ± 0.95and 1.8 ± 1.0, and for male and female non-patients at 0.26 ± 0.31 and 0.44 ± 0.54, respectively. Overall, women reported higher anxiety than men (0.76 ± 0.90 versus 0.57 ± 0.70, $p = 0.005$). This pattern of higher anxiety in women was seen in each country studied (Figure 2).

Analyses were performed to determine whether there was an interaction between sociodemographic or clinical variables and gender that would affect the relationship between gender and anxiety. These variables were age, marital status, education level, co-morbidities, pain level, clinical status on admission (i.e. admission vital signs and Killip classification), and medications (i.e. thrombolytics, beta-adrenergic blocking agents, and anxiolytics) used in the emergency department and during the hospitalization. None of these variables interacted with gender to produce an effect on anxiety.

To summarize, women are more anxious after early AMI than men and this finding is consistent across a variety of Western and Asian cultural groups. Women reported mean anxiety levels 25% higher than those reported by men, and twice as many women as men in the sample reported anxiety in the extreme ranges. The data also demonstrate that this higher level of anxiety is not the result of the influence of other sociodemographic or clinical characteristics on which men and women suffering AMI frequently differ. All patients should receive adequate assessment and management of

their anxiety, but it is important for clinicians to recognize those groups of patients who are at greater risk for higher anxiety. A fruitful area for future research includes investigation of reasons why women of different cultures all appear to be at higher risk for anxiety after AMI. Other important areas for investigation include determining whether higher anxiety after AMI contributes to the poorer prognosis seen in women, and determining the best methods for managing anxiety in busy hospitals. Despite the need for such research, the results of the present study are noteworthy for clinicians seeking to improve patient comfort and reduce the potentially harmful consequences of anxiety.

Relationship between anxiety and cardiac outcomes in CHD.

Despite anxiety being a common psychological response to a diagnosis of CHD or to an AMI, fewer investigators have examined the role of anxiety in cardiac outcomes than have examined the role of depression. Studies of the relationship of anxiety with CHD can be broadly grouped into the two following categories: 1) studies among initially healthy individuals who were followed to detect the occurrence of CHD; and 2) studies among patients with CHD who were followed to detect the occurrence or recurrence of CHD events (Table 4). Among the studies in initially healthy individuals, most(Eaker, Pinsky, & Castelli, 1992; Haines, Imeson, & Meade, 1987; Kawachi, Colditz et al., 1994; Kawachi, Sparrow, Vokonas, & Weiss, 1994) but not all(Martin, Cloninger, Guze, & Clayton, 1985) demonstrated that a variety of anxiety disorders (i.e. panic disorder, self-report phobic anxiety, and self-report anxiety symptoms) predicted future CHD mortality or AMI during a long follow-up period. This relationship was independent of the impact of other major cardiovascular risk factors and there was evidence of a dose-response effect.(Eaker et al., 1992; Haines et al., 1987; Kawachi, Colditz et al., 1994; Kawachi, Sparrow et al., 1994)

Although providing intriguing evidence of a link between anxiety in individuals without pre-existing disease and the development of CHD events, this body of work has been criticized for failure to control for factors other than cardiovascular risk factors that co-exist with anxiety and that in themselves might explain CHD independent of anxiety.(Bunker et al., 2003)

Among studies of the association between anxiety in people who already have CHD and the risk of subsequent CHD events, four have demonstrated that increased anxiety predicted subsequent CHD events (i.e. reinfarction, unstable angina, CHD mortality)(Denollet & Brutsaert, 1998; Frasure-Smith et al., 1995b; Herrmann et al., 1998; Moser & Dracup, 1996), three reported no association between anxiety and CHD outcomes(Lane et al., 2000a, 2000b; R. A. Mayou et al., 2000; Welin, Lappas, & Wilhelmsen, 2000), and one study reported that anxiety was associated with a survival *advantage*. (Herrmann, Brand-Driehorst, Buss, & Ruger, 2000) In all but one of these studies, subjects were patients hospitalized with AMI or other medical problem or undergoing CHD testing who were followed for months to years to examine CHD outcomes. In the exception, hospitalized AMI patients were followed only during their hospitalization to examine risk of in-hospital complications.(Moser & Dracup, 1996) In all studies, anxiety was assessed as self-reported symptoms. Although a variety of instruments were used among the studies, all instruments were standardized and psychometrically sound. In all studies, a number of factors were controlled so that the independent contribution of anxiety to CHD outcomes could be determined. Despite these similarities in efforts to insure rigor, this group of studies had different findings that left the research and clinical communities unsure of how to interpret the evidence of a

link between anxiety and CHD outcomes in individuals with pre-existing CHD.(Bunker et al., 2003) Thus, further research is needed in this area.

Relationship between anxiety and in-hospital complications in AMI patients

Few investigators have examined the relationship between anxiety and in-hospital complications in AMI patients. In order to clarify this issue, we conducted two studies designed to determine (1) the association between early anxiety in the AMI patient and the incidence of subsequent in-hospital AMI complications(Moser & Dracup, 1996); and (2) whether perceived control moderates any association between anxiety and in-hospital complications.(D. K. Moser, S. McKinley, B. Riegel, L. Doering, & B. Garvin, 2002)

In the first study, we assessed anxiety level using the anxiety subscale of the Brief Symptom Inventory within 48 hours of patient arrival at the hospital in 86 confirmed AMI patients. Information about in-hospital complications, including reinfarction, new onset ischemia, ventricular fibrillation, sustained ventricular tachycardia, or in-hospital death were also collected.

Anxiety level as assessed by the Brief Symptom Inventory in this sample of 86 AMI patients was 1.1 ± 0.93 (range 0 - 3.3). This is above the norm-referenced score of 0.35 and approaches the norm of 1.7 for psychiatric in-patients. Twenty-six (30%) patients scored at or below the norm of 0.35 while 22 (26%) scored at or above 1.7.

Complications were seen in 22 (25.6%) patients. Acute ischemia occurred in 12 (14%) patients, reinfarction in 4 (4.7%), sustained ventricular tachycardia in 9 (10.5%), ventricular fibrillation in 8 (9.3%), and in-hospital death in 3 (3.5%). The percentage of patients with complications by anxiety group is presented in Figure 3. Complications were seen in 19.6% of patients with higher anxiety versus 6% of patients with lower levels of

anxiety ($p = 0.001$). Of those patients with complications, one (4.5%) had an anxiety level below 0.35, 7 (41%) had an anxiety level between 0.35 and 1.7, and 9 (54.5%) had an anxiety level above 1.7.

Multiple logistic regression was used to control for those clinical and sociodemographic factors that can influence the incidence of complications and demonstrated that higher anxiety level was independently predictive of complications. Age, gender, Killip classification, thrombolytic therapy regimen and worst chest pain score were forced first into the logistic regression model, followed by anxiety. The introduction of anxiety significantly improved the model ($p = 0.001$). Only Killip classification (odds ratio 2.7, 95% CI 1.9 - 4.7, $p = 0.001$), and anxiety (odds ratio 4.9, 95% CI 2.1 - 12.2, $p = 0.003$) contributed significantly to the model. Patients with Killip class II as compared to Killip class I had 2.7 times the risk of complications as did patients with Killip class I. Controlling for the other factors, patients with higher anxiety (greater than 1.1 on the Brief Symptom Inventory) had 4.9 greater risk of complications than did patients with lower anxiety.

We conclude that anxiety early after myocardial infarction onset is associated with increased risk of ischemic and arrhythmic complications. This finding suggests that anxiety should be considered among the conventional risk factors for in-hospital acute myocardial infarction complications.

In the second study, we recruited a substantially larger sample and considered the interaction of perceived control with anxiety. We interviewed 536 patients with AMI (age 62 ±14, 34% female) within 72 hrs of admission. Anxiety was measured using the Brief Symptom Inventory and perceived control using the Cardiac Attitudes Scale.(Moser

& Dracup, 1995) Complications were defined as reinfarction, ischemia, ventricular tachycardia, ventricular fibrillation, or cardiac death. There were more complications in patients with high versus low anxiety ($p < 0.001$). In multivariate logistic regression analysis, higher anxiety was associated with increased risk for complications (odds ratio (OR) = 1.8, 95% confidence intervals (CI) 1.4—2.2; $p = 0.001$), independent of age, diabetes, previous AMI, type of AMI, and Killip class. The association between anxiety and complications was moderated by perceived control. For patients with low perceived control, 20% of low anxiety versus 80% of high anxiety patients had complications (OR = 2.0, 95% CI = 1.1 — 3.9, $p = 0.01$). In patients with high perceived control, there was no difference in risk ($p > 0.05$) based on anxiety level.

We concluded that anxiety predicts risk for complications in AMI patients, but this relationship is attenuated in those with high perceived control. Interventions that increase patient perception of control may help diminish the link between anxiety and poorer outcomes. However, the key to determining the optimal interventions for anxious cardiac patients is understanding the mechanisms linking anxiety with CHD outcomes.

Proposed mechanisms linking anxiety and CHD outcomes.

Although the mechanisms whereby anxiety might be associated with CHD outcomes are not entirely clear(Hachamovitch et al., 1995; Januzzi, Stern, Pasternak, & DeSanctis, 2000b), evidence suggests that there are two pathways linking anxiety and adverse CHD outcomes: 1) behavioral; and 2) physiologic (see Figure 4).(Carney, Freedland, & Stein, 2000; Frasure-Smith et al., 1995b; Januzzi et al., 2000a; Kubzansky & Kawachi, 2000; Kubzansky et al., 1998b; Lesperance & Frasure-Smith, 1996;

Rozanski et al., 1999a; Sheps & Sheffield, 2001; Sirois & Burg, 2003b; T. W. Smith & J. M. Ruiz, 2002)

Physiological mechanisms

Autonomic nervous system abnormalities.

Cardiac function is regulated by the two branches of the autonomic nervous system, the sympathetic nervous system (SNS) and the parasympathetic nervous system (PNS). The SNS and PNS differ in their anatomy and organization, neurotransmitters, and physiologic effects. In brief, physiologic stressors such as myocardial ischemia and psychological stressors such as anxiety activate the SNS, causing the release of two major catecholamines, epinephrine and norepinephrine. The heart is the first major organ to receive sympathetic input(Middlekauff, 1997; Rundqvist, Elam, Bergmann-Sverrisdottir, Eisenhofer, & Friberg, 1997) and the myocardium itself can synthesize norepinephrine.(Mann, 1999) Short-term, this so-called "fight or flight" phenomenon enables individuals to activate internal resources and counteract situations that threaten well-being.

Anxiety and the mental stress associated with it contribute to excessive SNS activation and catecholamine release.(Fehder, 1999) There is ample evidence in the literature that anxiety and mental stress activate the SNS for both healthy persons and individuals with poor health. For example, healthy men who were exposed to mental arithmetic and noise stressors had a higher heart rate, and elevated epinephrine and norepinephrine levels upon exposure to a stressor.(Sgoutas-Emch et al., 1994) Similarly, healthy males in another study exhibited an elevated heart rate and blood pressure during a speech stressor.(Baggett, Saab, & Carver, 1996) When exposed to mental stress, other

healthy persons demonstrated higher sympathetic activity as evidenced by significant changes in heart rate and heart rate variability measures.(Madden & Savard, 1995) For patients with CHD who underwent mental stress, there was a positive correlation between plasma epinephrine levels and changes in their heart rate, systolic blood pressure, and cardiac output.(Goldberg et al., 1996)

When considering individuals with cardiac disease, those with elevated anxiety or prolonged stress and a history of AMI had higher plasma norepinephrine levels than healthy volunteers, a finding that is consistent with SNS activation.(Kohn, Sleet, Carson, & Gray, 1983) Likewise, patients undergoing cardiac catheterization manifested higher norepinephrine, but not epinephrine, levels during mental stress testing.(Yeung et al., 1991)

In contrast to the SNS, the role of the PNS is to conserve and restore energy. It has been shown that both healthy volunteers with high anxiety and patients with generalized anxiety disorder have lower vagal tone than those with lower anxiety.(Thayer, Friedman, & Borkovec, 1996; Watkins, Grossman, Krishnan, & Sherwood, 1998) In turn, this weak vagal tone allows sympathetic activity to predominate.

Baroreceptors detect pressure and volume changes and either inhibit or excite the sympathetic and parasympathetic nervous systems. For example, if the baroreceptors sense hypotension, they stimulate the SNS, producing norepinephrine release, tachycardia, vasoconstriction, and contractility.

Only recently has anxiety been associated with impaired baroreflex sensitivity for cardiac patients. Watkins and colleagues reported that baroreflex control for patients

with AMI and high anxiety was about 20% lower than for patients with AMI and lower anxiety.(Watkins, Blumenthal, & Carney, 2002)

Cardiovascular reactivity (CVR) refers to a "generalized propensity to respond to behavioral stimuli with cardiovascular reactions of a certain magnitude."(Manuck, 1994) For example, patients with exaggerated CVR experience frequent, pronounced, and sustained changes in BP, HR, stroke volume, and total peripheral resistance. Increased CVR may be contribute to the development of cardiac disease(Timothy W. Smith & John M. Ruiz, 2002) and be a useful in identifying postinfarction patients who are at risk for reinfarction or stroke.(Manuck, Olsson, Hjemdahl, & Rehnqvist, 1992)

Proposed models of the relationship between psychological influences and heart disease generally emphasize the role of the autonomic nervous system.(Kamarck & Jennings, 1991; Kop, 1999; Krantz, Kop, Santiago, & Gottdiener, 1996) One pathophysiologic model accounts for the relationships between acute, episodic, and chronic psychological factors and coronary artery disease.(Kop, 1999) According to the model, acute psychological factors, such as anger and mental activity, stimulate autonomic nervous system activity which in turn triggers production of catecholamines, increases HR and BP, decreases plasma volume, constricts coronary arteries, and increases cardiac demand, platelet activity, coagulation, and inflammation. As a result, patients are more prone to thrombogenesis, arrhythmogenesis, altered heart rate variability, increased myocardial oxygen demand, myocardial ischemia, and impaired ventricular function.

Thrombogenesis

High anxiety may contribute to platelet aggregation and recurrent thrombus formation.(Frasure-Smith, Lesperance, & Talajic, 1995a; Hjemdahl, Larsson, & Wallen, 1991) Evidence suggests that both epinephrine and norepinephrine function as platelet agonists(Frasure-Smith et al., 1995a; Markovitz & Matthews, 1991) and that epinephrine accelerates hemostasis and fibrinolysis.(von Kanel, Mills, Fainman, & Dimsdale, 2001) During mental stress, healthy volunteers had higher norepinephrine and epinephrine levels, increased platelet activation, increased hematocrit levels, and a lower plasma volume.(Patterson et al., 1995) In another study of healthy volunteers, mental stress also increased coagulation and stimulated the fibrinolytic system.(Jern et al., 1989)

Similar results have been reported for patients with cardiac disease. When exposed to mental stress, patients with AMI experienced increased platelet aggregation, formed more circulating platelet aggregates, and developed higher plasma and serum thromboxane B_2 levels than healthy controls.(Grignani et al., 1991) Patients with angina who underwent mental stress testing tended towards platelet activation more than healthy controls.(Wallen, Held, Rehnqvist, & Hjemdahl, 1997) In a review paper, von Kanel concluded that patients with atherosclerosis who experience mental stress may tend towards hypercoagulation due to endothelial dysfunction and reduced fibrinolysis.(von Kanel et al., 2001) Ghiadoni and associates reported that healthy persons developed endothelial dysfunction for up to 4 hours after exposure to mental stress.(Ghiadoni et al., 2000)

Arrhythmogenesis

Enhanced sympathetic stimulation is one cause of cardiac dysrhythmias for patients with cardiac disease.(Lown & Verrier, 1976; Lown, Verrier, & Rabinowitz,

1977; Middlekauff & Mark, 1998) Additionally, acute psychological insults are capable of causing lethal ventricular dysrhythmias.(Brodsky, Sato, Iseri, Wolff, & Allen, 1987; Lown, 1987; Lown et al., 1977) In research conducted prior to routine beta blocker use for AMI, patients with AMI and either ventricular dysrhythmias or sinus tachycardia had increased circulating catecholamine levels.(Nadeau & de Champlain, 1979) Patients with frequent ventricular ectopy but no history of AMI were more anxious than age- and sex-matched medical-surgical patients.(Katz, Martin, Landa, & Chadda, 1985) An association between high anxiety and prolonged QTc intervals has been reported and may place high risk for lethal cardiac dysrhythmias.(Fava, Abraham, Pava, Shuster, & Rosenbaum, 1996)

Several researchers induced mental stress for patients with heart disease. Patients with ventricular dysrhythmias had more ectopy during a mildly stressful interview than during control time periods.(Lown, DeSilva, Reich, & Murawski, 1980) In another study, patients had significantly more ventricular dysrhythmias during psychological stress testing than during a control period.(Lown, 1987) For patients with AMI, mental stress contributed to a shorter mean ventricular refractory period and the onset of nonsustained ventricular tachycardia.(Tavazzi, Zotti, & Rondanelli, 1986)

Increased myocardial oxygen demand

Mental stress increases heart rate and upsets the balance between myocardial oxygen supply and demand.(Cordero, Cagin, & Natelson, 1995; Rozanski, Krantz, & Bairey, 1991b) Many investigators have documented that mental stress increases heart rate;(Kop et al., 2001; Lacy et al., 1995; LaVeau et al., 1989; Mazzuero et al., 1989; Okano, Utsunomiya, & Yano, 1998; Sgoutas-Emch et al., 1994; Yeung et al., 1991)

however, whether these increases are clinically distinguishable or significant remains questionable. Others reported that vascular resistance increased when patients with heart disease where exposed to mental stress but decreased in normal controls.(Jain et al., 1998) Remarkably, patients with heart disease have exhibited larger increases in SVR during mental stress than during exercise.(Goldberg et al., 1996) In review papers, Rozanski and colleagues compared mental stress-induced ischemia with exercise-induced ischemia, pointing out that that mental stress-induced ischemia is often associated a sudden onset, smaller HR elevation, higher blood pressure, and lower double product (heart rate x systolic blood pressure).(Rozanski, Blumenthal, & Kaplan, 1999b; Rozanski et al., 1991b)

Myocardial ischemia

Mental stress is a potent trigger of myocardial ischemia.(Krantz et al., 1996; Mittleman et al., 1995) In fact, mental stress can induce ischemia at lower levels of cardiac demand than exercise(Kop, 1999; L'Abbate, Simonetti, Carpeggiani, & Michelassi, 1991; Rozanski et al., 1999b) and even has caused complete coronary artery occlusion(Papademetriou, Gottdiener, Kop, Howell, & Krantz, 1996) and AMI.(Gelernt & Hochman, 1992) Of note, is that patients often report that stress caused their AMI.(Marmot, 1986; Wielgosz & Nolan, 2000)

For patients with atherosclerosis, a catecholamine surge can cause myocardial ischemia due to increased myocardial oxygen demand.(Krantz et al., 1996) Patients with AMI were more anxious 0-2 hours before their AMI than 24-26 hours before the AMI.(Mittleman et al., 1995) In a review paper, Kubzansky and associates pointed out

that anxiety may cause rapid blood pressure changes and subsequent atherosclerotic plaque rupture.(Kubzansky, Kawachi, Weiss, & Sparrow, 1998a)

Mental stress should trigger coronary vasodilation due to increased myocardial oxygen demand; however, this compensatory mechanism was absent in patients with CAD.(Dakak, Quyyumi, Eisenhofer, Goldstein, & Cannon, 1995) Indeed, mental stress has also been shown to vasoconstrict coronary arteries and decrease coronary flow velocity in patients with CAD.(Kop et al., 2001) Yeung and colleagues reported that stenosed or irregular coronary artery segments significantly constricted in response to mental stress, whereas smooth segments remained unchanged or dilated.(Yeung et al., 1991) Legault and colleagues reported that 49% of the patients experienced stress-induced ischemia and concluded that patients with more severe coronary artery stenoses were the most likely to experience stress-induced ischemia.(Legault, Freeman, Langer, & Armstrong, 1995) Furthermore, mental stress has been shown to cause coronary artery vasoconstriction of even normal coronary artery segments for patients with and without CAD.(Lacy et al., 1995) In contrast, others found that neither normal nor stenotic coronary artery segments changed diameter in response to mental stress.(L'Abbate et al., 1991)

Although the mechanism is not entirely clear, experts have proposed that endothelial dysfunction makes the coronary arteries more sensitive to the constrictor effects of catecholamines.(Vita et al., 1992) Mental stress increases catecholamine levels and thus, in the setting of endothelial dysfunction, can cause coronary constriction.(Papademetriou et al., 1996) Interestingly, others documented that during mental stress, coronary flow reserve was lower in myocardial regions without significant

epicardial stenosis than in regions with significant stenosis, a finding that also may reflect microvascular dysfunction.(Arrighi et al., 2000)

Stress-induced ischemic events may occur at relatively low and commonly experienced heart rates and may go unnoticed by patients.(Mazzuero et al., 1989) Patients who underwent coronary angiography experienced two time periods of stress – a more stressful period during which they awaited results of their procedure and a less stressful period during which they had time to adjust to their diagnosis and treatment plan.(Freeman, Nixon, Sallabank, & Reaveley, 1987) There were more episodes of silent ischemia during the more stressful time period. Furthermore, patients with a higher norepinephrine level had more of these episodes and experienced longer total ischemic times. When compared to patients without silent ischemia, patients with ischemia reported more social dysfunction, anxiety, dysphoria, and severe depression during the stressful time period.

Finally, patients may hyperventilate in response to acute anxiety. Rasmussen and colleagues reported that hyperventilation can induce coronary artery spasm, a condition that impairs coronary blood flow.(Rasmussen, Ravnsbaek, Funch-Jensen, & Bagger, 1986)

In their review paper, Strike and Steptoe emphasized five points: 1) patients with heart disease are more likely to experience mental stress-induced myocardial ischemia (MSIMI), 2) patients with MSIMI are usually asymptomatic, 3) most patients with MSIMI also experience exercise-induced ischemia, 4) the rates of reported MSIMI are highly variable, and 5) most research had been conducted with male patients.(Strike &

Steptoe, 2003) Mental stress-induced ischemia is an important predictor of poor prognosis.(Strike & Steptoe, 2003)

Impaired ventricular function

When patients with CHD and exercise-induced wall-motion abnormalities were exposed to a mental stressor, 72% demonstrated stress-induced wall-motion abnormalities that were similar to exercise-induced wall-motion abnormalities.(Rozanski et al., 1988a) Additionally, 36% of these patients had a 5% or greater drop in their ejection fraction. Yet, 83% of these ischemic patients were asymptomatic and thus, unaware of their worsened condition. In another study, 53% of patients with CHD developed a new wall-motion abnormality when exposed to stress.(Gottdiener et al., 1994) In another study, patients with cardiac disease whose ejection fraction did not increase by 5% or more during exercise experienced a lower ejection fraction during mental stress.(LaVeau et al., 1989) With exposure to mental stress, patients with AMI developed impaired ventricular function as evidenced by a significant increase in pulmonary capillary wedge pressure and decrease in stroke volume.(Mazzuero, Temporelli, & Tavazzi, 1991) Similarly, others reported wall motion abnormalities or decreased EF with mental stress.(Bairey, Krantz, & Rozanski, 1990; Burg, Jain, Soufer, Kerns, & Zaret, 1993; Goldberg et al., 1996; Jain et al., 1998; Kuroda et al., 2000; LaVeau et al., 1989; Legault et al., 1995; Mazzuero et al., 1989)

Mental stress affects not only systolic function, but also diastolic function. Patients with CAD experienced diastolic dysfunction and increases in BP, HR, and rate pressure product during a mental stressor.(Okano et al., 1998) Interestingly, this diastolic dysfunction was neither accompanied by systolic dysfunction nor ST segment ECG

changes. In another study, patients with HF showed evidence of increased ventricular stiffness and high left ventricular filling pressures during mental stress.(Giannuzzi et al., 1991)

The effects of mental stress extend beyond research settings. Patients with cardiac disease routinely experience stressful situations during the course of everyday life. Blumenthal and colleagues found that patients who developed ischemia and wall motion abnormalities in response to mental stress in a laboratory setting were more likely to experience ambulatory ischemia.(Blumenthal et al., 1995)

Patients with CAD were exposed to a series of mental stresses followed by a physical stressor. During the mental stressor, 21 of 29 (72%) patients with exercise-induced wall-motion abnormalities also demonstrated stress-induced wall-motion abnormalities. Additionally, 36% of the participants had a 5% or greater drop in their ejection fraction.(Rozanski et al., 1988a) The majority (65%) of patients with exercise-induced wall-motion changes also developed mental-induced wall-motion changes.

Behavioral mechanisms

Experts have hypothesized that behavioral mechanisms are another link between anxiety and cardiac disease. Compared to nonanxious individuals, those with high anxiety may eat an unhealthy diet,(Buselli & Stuart, 1999; Hayward, 1995; Sirois & Burg, 2003a) smoke,(Buselli & Stuart, 1999; Hayward, 1995; Kubzansky et al., 1998a; Sirois & Burg, 2003a) consume drugs or alcohol,(Buselli & Stuart, 1999; Sirois & Burg, 2003a) fail to adhere to therapy,(Frasure-Smith et al., 1995a) sleep poorly,(Buselli & Stuart, 1999; Sirois & Burg, 2003a) and be physically inactive.(Buselli & Stuart, 1999; Hayward, 1995; Sirois & Burg, 2003a) These harmful behaviors are associated with the

incidence and progression of cardiac disease.(Buselli & Stuart, 1999) Far less is known about the potential behavioral mechanisms linking anxiety with adverse cardiac outcomes.

Summary.

Anxiety is common among cardiac patients and should be treated to enhance recovery and decrease patients' risk of subsequent cardiac events. One of the most important areas for future research is elucidating the mechanisms whereby anxiety causes poorer outcomes in AMI patients. The mechanisms (either physiological or behavioral) whereby anxiety is related to poorer short and long term outcomes in AMI patients have yet to be elucidated. Research in this area is important to help clinicians determine the best ways to manage AMI patients to decrease the negative impact of anxiety. Without understanding the basic underlying mechanisms, it is difficult to know whether treatment should concentrate on pharmacological strategies such as beta-blocker therapy to decrease sympathetic nervous system responses to anxiety or more directly on anti-anxiety drug therapy. The role of nonpharmacologic strategies that decrease psychophysiologic arousal also should be investigated.

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Table 1: Sociodemographic Characteristics in an International Sample of 912 Acute Myocardial Infarction Patients

Characteristic	**Entire Sample N = 912**	**Australia n = 127**	**England n = 144**	**Japan n = 136**	**South Korea n = 128**	**United States n = 377**
Age, mean ± standard deviation, years*	61 ± 13	62 ± 13	61 ± 13	61 ± 11	57 ± 11	62 ± 14
Education, mean ± standard deviation years#	12 ± 4	13 ± 4	10 ± 4	13 ± 3	11 ± 5	13 ± 3
Male, n (%)§	658 (72.1)	101 (79.5)	111 (77.1)	109 (80.1)	99 (77.3)	238 (63.1)
Marital status, n (%)						
Married†	684 (75)	87 (68.5)	108 (75)	117 (86)	117 (91.4)	255 (67.6)
Divorced/widowed/ single	220 (24.1)	40 (31.5)	33 (22.9)	19 (14)	10 (7.8)	118 (31.3)

* $P = .02$, South Korea < every other country; # $P = .004$, England and South Korea < every other country; § $P = .001$ U.S, < every other country; † $P = .001$, Japan and South Korea > every other country

Table 2: Clinical Characteristics in an International Sample of 912 Acute Myocardial Infarction Patients

Characteristic	**Entire Sample** N = 912 N (%)	**Australia** n = 127 n (%)	**England** n = 144 n (%)	**Japan** n = 136 n (%)	**South Korea** n = 128 n (%)	**United States** n = 377 n (%)
Current smoker*	419 (45.9)	39 (30.7)	64 (44.4)	93 (68.4)	87 (68)	136 (36.1)
Hypertension#	482 (52.9)	48 (37.8)	59 (41)	74 (54.4)	62 (48.4)	239 (63.4)
Diabetes mellitus§	225 (24.7)	12 (9.4)	37 (25.7)	47 (34.6)	31 (24.2)	98 (26)
Previous AMI#	192 (21.1)	17 (13.4)	29 (20.1)	21 (15.4)	10 (7.8)	115 (30.5)
Killip class						
I†	604 (66.2)	99 (78)	104 (72.2)	116 (85.3)	78 (60.9)	207 (54.9)
II	229 (25.1)	21 (16.5)	29 (20.1)	13 (9.6)	37 (28.9)	129 (34.2)
III-IV	72 (7.9)	7 (5.5)	10 (7)	6 (4.4)	13 (10.2)	36 (9.6)

Treatment in ED						
Fibrinolytic‡	310 (34.4)	34 (26.8)	99 (68.8)	20 (14.7)	36 (28.8)	121 (32.7)
Beta Blocker**	320 (35.1)	28 (22.0)	72 (50.0)	11 (8.1)	10 (7.8)	199 (52.8)
Aspirin##	715 (78.4)	103 (81.1)	138 (95.8)	71 (52.2)	103 (80.5)	300 (79.6)
Anxiolytic#	270 (29.6)	30 (23.6)	43 (29.9)	28 (20.6)	33 (25.8)	136 (36.1)

AMI = acute myocardial infarction; ED = emergency department

* $P = .001$, Japan and South Korea > every other country; # $P = .001$, U.S. > every other country; § $P = .001$, Australia < every other country; † $P = .001$, Japan > every other country; ‡ $P = .001$, England > every other country; ** $P = .001$, U.S. and England > Australia > Japan and South Korea; ## $P = .001$, England > U.S., Australia, South Korea > Japan

Table 3: Demographic and clinical characteristics compared between genders in an international sample of 912 acute myocardial infarction patients

	Australia (n = 127)		England (n = 144)		Japan (n = 136)		South Korea (n = 128)		United States (n = 377)	
	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female
Age (years)*	60.2 ± 12.6	71.1 ± 1185	59.3 ± 13.3	66.6 ± 13.9	59.4 ± 11.4	66.0 ± 9.1	54.7 ± 10.8	64.7 ± 10.3	59.1 ± 13.3	65.6 ± 13.2
Education (years)&	14.7 ± 13.5	10.9 ± 2.5	10.5 ± 4.1	8.4 ± 4.4	13.4 ± 3.0	10.8 ± 2.6	12.3 ± 4.3	8.3 ± 4.1	13.3 ± 2.9	12.9 ± 2.9
% married¶	76%	39%	82%	59%	87%	82%	96%	79%	77%	54%
Admission systolic BP (mmHg)@	138.6 ± 27.5	140.3 ± 24.5	142.3 ± 28.5	143.1 ± 32.2	131.1 ± 27.3	128.2 ± 23.6	129.5 ± 30.4	124.1 ± 28.3	141.6 ± 27.8	142.3 ± 28.8
Admission diastolic BP (mmHg)@	79.8 ± 15.9	79.8 ± 18.4	88.2 ± 21.3	88.2 ± 23.3	76.8 ± 15.6	74.5 ± 12.6	79.7 ± 17.6	77.5 ± 21.2	83.2 ± 17.5	81.2 ± 16.3
Admission	73.3 ± 22.5	80.4 ± 15.2	78.4 ± 19.2	80.8 ± 25.8	78.8 ± 20.4	76.0 ± 25.7	75.4 ± 16.1	73.8 ± 19.6	77.7 ± 18.2	83.3 ± 22.2

Worst AMI pain (0 – 10)#	6.8 ± 2.4	6.7 ± 2.9	7.7 ± 2.3	7.8 ± 2.8	7.5 ± 3.0	7.5 ± 3.0	7.9 ± 2.7	7.2 ± 2.6	6.9 ± 2.6	7.1 ± 2.6

Table 1 legend: AMI – acute myocardial infarction; BP = blood pressure; ED = emergency department; * = gender differences in age for all countries ($p < 0.01$); & = gender differences in education level for all countries ($p < 0.01$); # = gender difference in admission pulse ($p = 0.009$) and highest pain level ($p = 0.01$) in USA only; ¶ = gender differences for all countries ($p < 0.05$) except Japan; @ = no gender differences

Table 4: Studies of the relationship between anxiety and CHD outcomes			
Authors	***Sample Size***	***Outcome Tested***	***Results***
Studies in initially healthy individuals			
Martin et al., 1985(Martin et al., 1985)	60 psychiatric outpatient men and women, 7 years follow-up	CHD mortality	Anxiety not associated with outcome
Haines et al., 1987(Haines et al., 1987)	1457 community-dwelling men, 10 years follow-up	CHD mortality	RR of event for anxious = 3.77; dose response evident
Weissman, 1990(Weissman, Markowitz, Ouellette, Greenwald, & Kahn, 1990)	3778 healthy men and women, follow-up period not reported	AMI	RR of event for anxious = 4.5
Eaker et al., 1992(Eaker et al., 1992)	749 community dwelling women, 20 years follow-up	CHD events	RR of event for anxious = 7.8
Kawachi et al., 1994 (Kawachi, Colditz et al., 1994)	33,999 health professional men, 2 years follow-up	CHD mortality	RR of event for anxious = 2.45; dose response evident

Kawachi et al., 1994(Kawachi, Sparrow et al., 1994)	2280 community dwelling men, 32 years follow-up	Sudden death	RR of event for anxious = 4.46; dose response evident
Studies in patients with CHD			
Frasure-Smith et al., 1995(Frasure-Smith et al., 1995b)	220 AMI patients, 1 year follow-up	CHD events	RR of event for anxious = 2.5
Moser et al., 1996(Moser & Dracup, 1996)	86 AMI patients, in-hospital study	Recurrent ischemia, reinfarction, ventricular arrhythmias, death	RR of event for anxious = 4.9
Denoillet et al., 1998(Denollet & Brutsaert, 1998)	87 AMI patients, 7.9 years follow-up	MI, cardiac death, unstable angina, sudden death event	RR of event for anxious = 3.9
Herrmann et al., 1998(Herrmann et al., 1998)	454 patients with medical conditions; 273 CP, 1.9 years follow-up	All-cause mortality	RR of event for anxious = 2.9
Herrmann et al.,	5057 men and women	All-cause mortality	RR of event for anxious = 0.75

2000(Herrmann et al., 2000)	referred for exercise testing (49% CHD), 5.7 years follow-up		*(increased anxiety associated with increased survival)*
Welin et al., 2000(Welin et al., 2000)	255 men and women with MI, 10 years follow-up	CHD and all-cause mortality, recurrent infarction	Anxiety not associated with outcome
Mayou et al., 2000(R. A. Mayou et al., 2000)	347 men and women with MI, 18 month follow-up	CHD mortality	Anxiety not associated with CHD mortality
Lane et al., 2000(Lane et al., 2000a, 2000b)	288 men and women with MI, 4 & 12 month follow-up	CHD and all-cause mortality	Anxiety not associated with mortality outcomes
AMI = acute myocardial infarction; CHD = coronary heart disease; CP = cardiopulmonary; RR = relative risk; MI = myocardial infarction			

Figure Legends

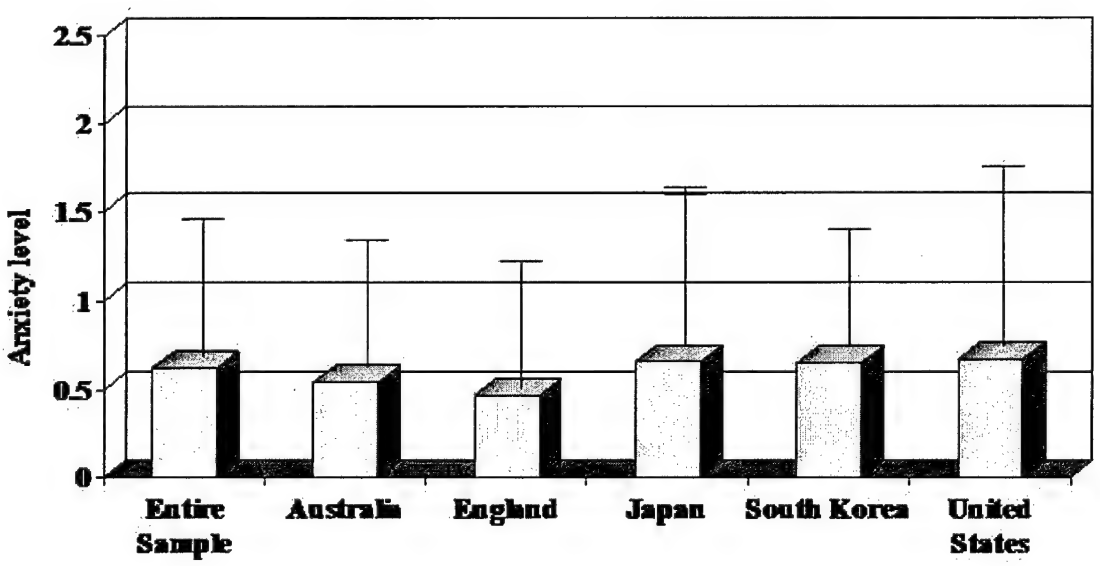
Figure 1: Mean anxiety levels (with standard deviations) in 912 acute myocardial infarction patients in five countries

Figure 2: Gender differences in anxiety overall and in each country

Figure 3: Comparison of complication rates between acute myocardial infarction patients with low versus high levels of anxiety

Figure 4: Potential mechanisms linking anxiety with coronary heart disease events

Figure 1


2.5
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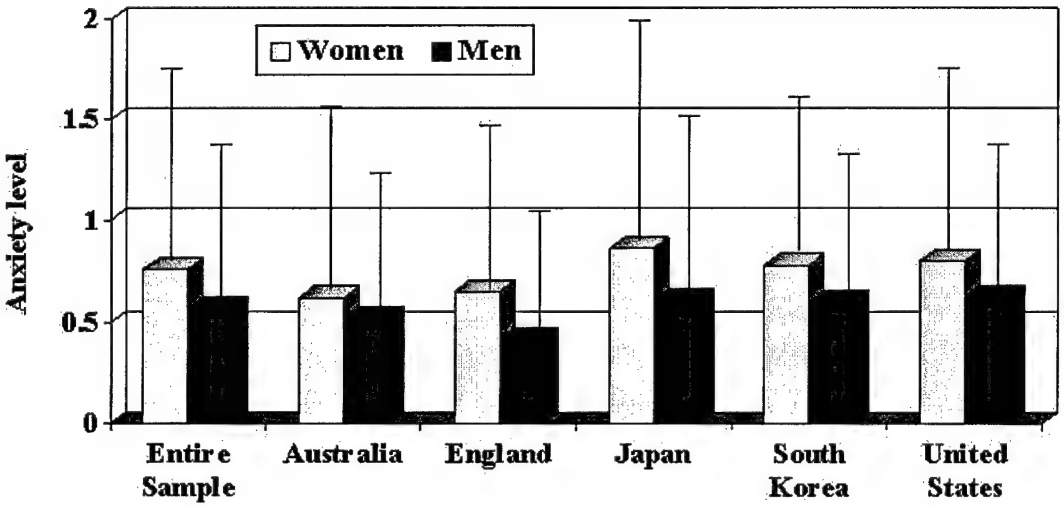
Anxiety level
Entire Sample
Australia
England
Japan
South Korea
United States

Figure 2


Women
Men
Anxiety level
2
1.5
1
0.5
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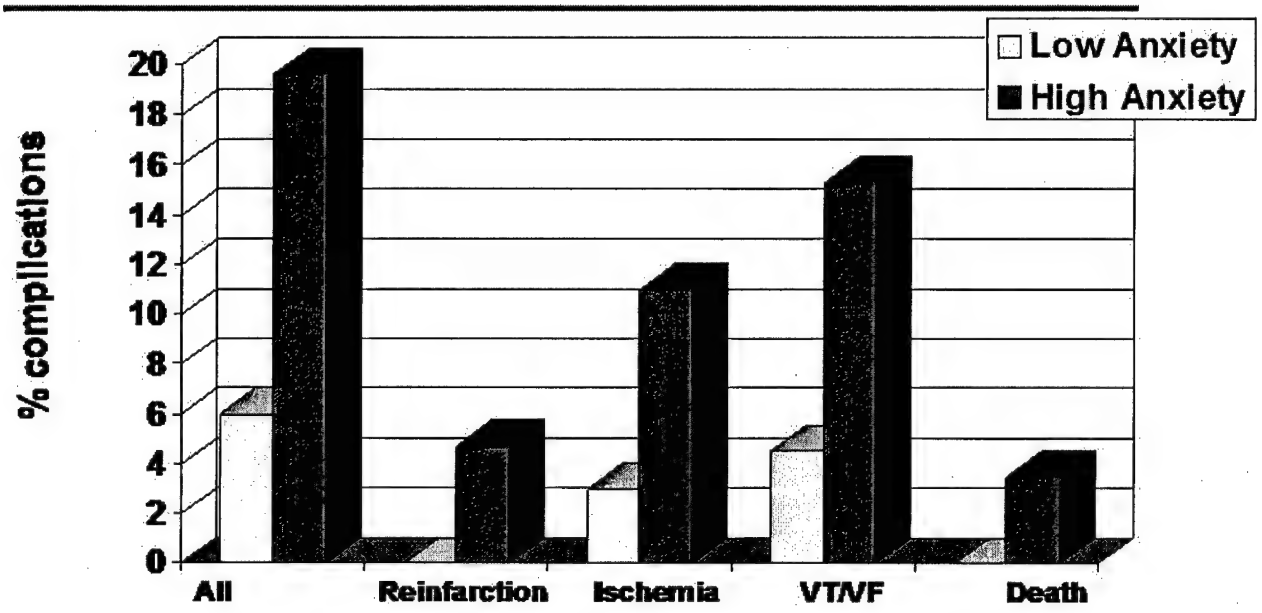
Entire Sample
Australia
England
Japan
South Korea
United States

Figure 3


Low Anxiety
High Anxiety
% complications
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14
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10
8
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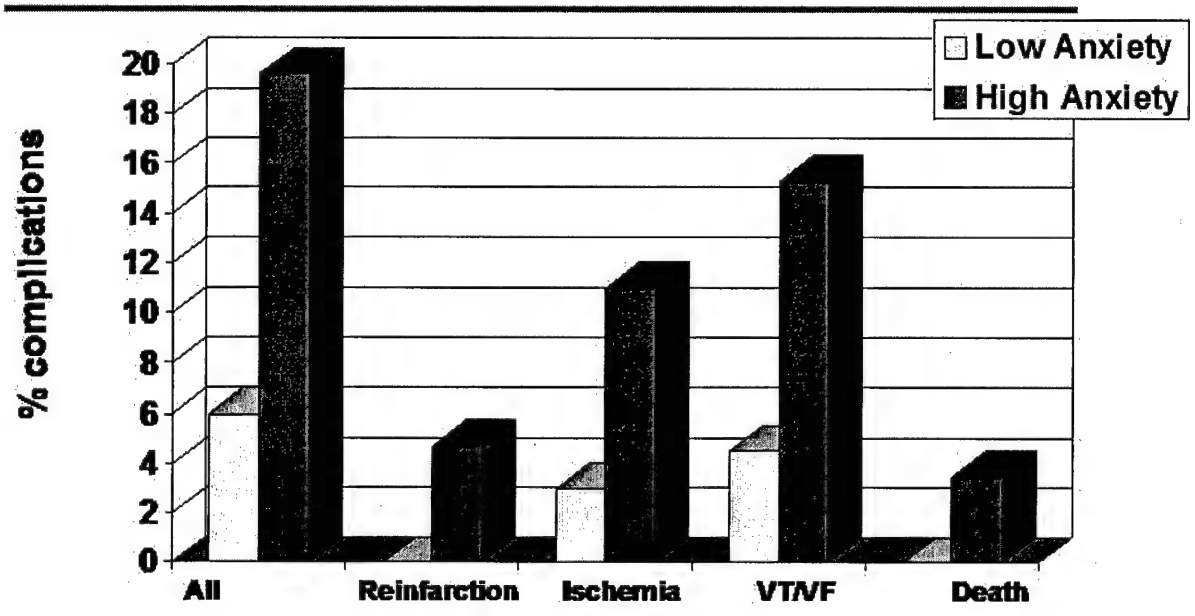
0
All
Reinfarction
Ischemia
VT/VF
Death


Low Anxiety
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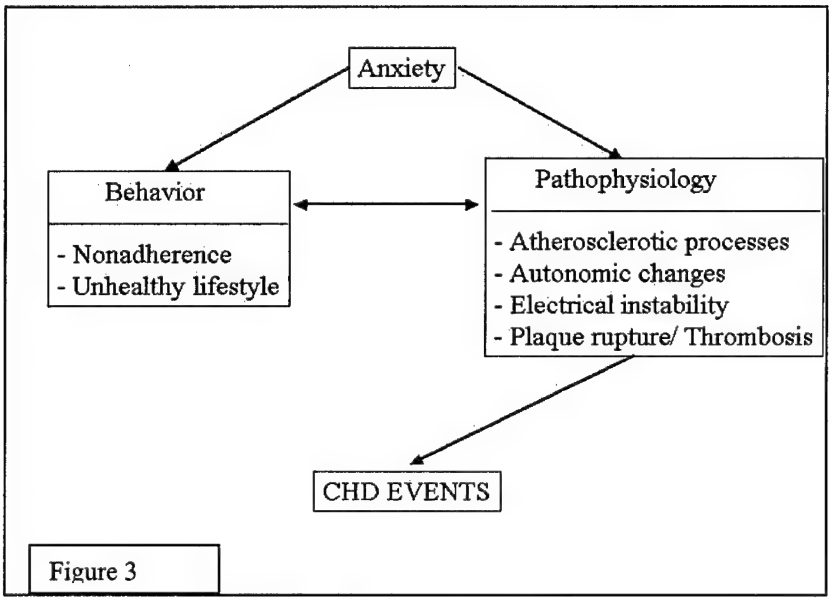
VT/VF
Death

Figure 4



Legend: CHD = coronary heart disease events

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